Remarks

Claims 1-38 are pending in the subject application. Applicants acknowledge that claims 10-13, 16-36, and 38 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have canceled claims 10-13, 16-36, and 38 and amended claims 1, 7-9, and 14. Support for the amendments can be found throughout the subject specification. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-9, 14, 15, and 37 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants have amended the subject specification to include an "Abstract of the Disclosure" page. Support for the disclosure in Abstract can be found throughout the subject specification. Applicants respectfully assert that no new matter is included in the Abstract.

Claims 1-9, 14, 15, and 37 are objected to because they recite non-elected subject matter. In addition, claims 14, 15, and 37 are objected to because they recite the phrase "and/or." Applicants have amended the claims to delete reference to non-elected subject matter and have replaced the phrase "and/or" in claim 14 with "one or both of" in accordance with the Examiner's helpful suggestion. Accordingly, reconsideration and withdrawal of the objections is respectfully requested.

Claims 1-9, 14, 15, and 37 are rejected under 35 USC §112, first paragraph, as nonenabled by the subject specification. The Examiner asserts that the subject specification does not enable treatment of any vascular disorder other than intimal hyperplasia in any species other than a rabbit using a DNA expression vector encoding a VEGF receptor agonist which is not an agonist for both Flt-1 and FLK-1/KDR receptors. Applicants respectfully assert that the claims are enabled by the subject specification.

In regard to the aspect of the rejection directed to the variety of "VEGF receptors and receptor agonists," Applicants respectfully assert that the claims are enabled for all VEGF receptors and receptor agonists are known in the art.

In regard to the aspect of this rejection directed to "nucleic acid mediated therapy and *in vivo* vector targeting," Applicants respectfully assert that the present invention is enabled for delivery and expression of a nucleic acid in a target cell. Attached with this Amendment is a Declaration Under

37 CFR 1.132 by Dr. John Francis Martin (unsigned) which shows that nucleic acid encoding a VEGF receptor agonist was delivered and expressed in targeted blood vessel cells. Applicants will provide the executed Declaration to the Examiner under separate cover. Applicants note that the Examiner acknowledges in the outstanding Office Action that the specification does support direct application of nucleic acids to the treatment site of the blood vessel. Applicants note that claim 1 has been amended to clarify that the nucleic acid is provided at the site of the blood vessel being treated. Accordingly, Applicants respectfully assert that the claimed invention is enabled for delivery and expression of a nucleic acid to a target cell or tissue.

In regard to the aspect of the rejection directed to "hypertension and diseases related to NO and prostacyclin production," Applicants respectfully assert that the subject specification does enable treatment of conditions that can be treated or prevented by stimulation of nitric oxide and/or prostacyclin production via the administration of a nucleic acid that encodes an agonist of a VEGF receptor. Under the authority of *In re Marzocchi*, 169 USPQ 367 (CCPA 1971), Applicants' statements must be taken as true unless the Patent Office can recite specific reasons to doubt the validity of those statements. The Examiner has failed to provide any specific evidence that the claimed invention would not have efficacy in treating hypertension and other diseases that can be affected by or that are associated with nitric oxide and prostacyclin production.

In regard to the aspect of the rejection directed to "relevance of animal models of intimal hyperplasia to human disease and treatment," the first reference on which the Examiner relies is Muller *et al.* (1992). The Examiner asserts that this reference suggests that small animal models may not be predictive of success in humans. In particular, the Examiner indicates that according to Muller *et al.*, none of the agents tested in the animal models reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. As will be further discussed in Applicants' remarks addressing the prior art rejections, the present invention is unrelated to reducing the incidence of restenosis after coronary balloon angioplasty. Coronary balloon angioplasty destroys the epithelium. In contrast, the present invention involves the treatment or prevention of intimal hyperplasia, where the endothelium is wholly or largely intact. Thus, Applicants respectfully assert that the results disclosed in the Muller *et al.* reference are not relevant to the subject invention.

On page 13 of the Office Action, the Examiner suggests that the enabled use of the invention is limited to rabbits. Applicants respectfully assert that the scope of the claimed invention is not limited to the treatment of rabbits. In the attached Declaration, Dr. Martin summarizes Applicants' pre-clinical data for the use of VEGF in the treatment of intimal hyperplasia. This data was recently presented to the Recombinant Gene Advisory Committee of the National Institutes of Health, and the Food & Drug Administration, as part of the process for obtaining approval to perform clinical trials. Applicants submit that the information relating to the pig study described in Dr. Martin's Declaration is particularly relevant, as it shows that VEGF can have an effect across species. In this case, the Food & Drug Administration suggested the use of pig data for purposes of predicting suitability for human clinical trials. Thus, Applicants respectfully assert that the claimed invention is enabled for use with mammalian species, including humans.

In view of the above remarks, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 1-9, 14, 15, and 37 are rejected under 35 USC §112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. However, in order to lend greater clarity to the claimed subject matter, Applicants have amended the claims. Specifically, Applicants have amended claim 1 to delete reference to "wholly or largely." However, Applicants respectfully assert that the claims, as amended, encompass situations where the epithelium is reduced in thickness. Applicants also respectfully assert that there is antecedent basis for the term "endothelium" in claims 1-9. The term "endothelium" is specifically recited in line 2 of claim 1. However, Applicants have amended claim 1 to clarify that the "endothelium" is that of the blood vessel being treated.

In regard to the rejection of claim 7, Applicants have amended the claim to delete reference to "function of human VEGF." In regard to the rejection of claim 8, Applicants respectfully assert that the claim encompasses those fragments of the sequences that are biologically active. Any biological activity of VEGF is contemplated in the subject invention. The ordinarily skilled artisan can readily prepare fragments of a VEGF protein and determine whether that fragment exhibits a VEGF biological activity. In view of the above remarks and amendments to the claims, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 1-9, 14, 15, and 37 are rejected under 35 USC §102(e) as anticipated by Isner (U.S. Patent No. 6,121,246) or Isner (U.S. Patent No. 6,258,787). The Examiner asserts that the '246 patent teaches a method for inducing formation of new blood vessels by injecting into a human host an effective amount of a DNA sequence encoding vascular endothelial growth factor (VEGF). The Examiner further asserts that the '787 patent is cited as teaching a method for inducing re-endothelialization in a blood vessel by administration of a nucleic acid encoding VEGF, wherein the blood vessel comprises a portion which is denuded of its epithelial lining. Applicants respectfully traverse both grounds of rejection.

Applicants respectfully assert that the Isner patents do not anticipate the claimed invention. Applicants note that the Examiner states the '787 patent teaches that "the blood vessel may be partially denuded of its endothelium by use of an arterial balloon catheter." The Examiner attempts to reduce the effect of this statement by further indicating that "the endothelium of the rest of the blood vessel should remain largely intact." However, Applicants respectfully assert that denudation is the inevitable consequence of the use of an arterial balloon catheter and that the ordinarily skilled artisan would not have appreciated, and the art did not teach or suggest, that there might be any beneficial effect on a non-denuded vessel.

Presumably, the intended effect of the treatment disclosed in the cited patents is reendothelialization. Applicants' invention provides for treatment following reendothelialization. There is no teaching or suggestion in the cited patents to administer VEGF once reendothelialization has occurred. To the contrary, it seems likely that the patentees of the cited patents assumed that intimal hyperplasia was attenuated because of reendothelialization.

The present invention is based on the direct utility of VEGF, *via* a different mechanism. As explained in the subject specification, this provides for useful therapy that was not taught and could not have been predicted from the prior art. In the absence of teaching each and every element of Applicants' claimed invention, the cited patents do not anticipate the claims. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §102(e) is respectfully requested.

Claims 1-9, 14, 15, and 37 are rejected under 35 USC §102(a) as anticipated by Isner (1996) or Takeshita *et al.* (1996). The Examiner indicates that the Isner *et al.* and Takeshita *et al.* references teach a method of inducing formation of new blood vessels by injecting into a human host an

effective amount of a DNA sequence encoding VEGF-165. Applicants respectfully traverse both grounds of rejection.

Applicants respectfully assert that the cited references do not anticipate the claimed invention. The recitation in Applicants' claimed methods that the endothelium is intact distinguishes the claimed methods from the Isner and Takeshita references. Whereas VEGF has a known role in angiogenesis and regrowth of endothelium after angioplasty, the present invention is based on the discovery that VEGF can be used to prevent or treat *de novo* stenosis in other surgical situations. As the Examiner is aware, in order to anticipate, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). The cited references fail to teach methods wherein the endothelium of the blood vessel is wholly or largely intact. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §102(a) is respectfully requested.

It should be understood that these amendments have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRP/sl
Attachments: Marked-Up Version of Amended Claims; Abstract of the Disclosure; Declaration of Dr. John Francis Martin Under 37 CFR 1.132 (unsigned).

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ORIGINALLY FILED

Docket No. GJE-30
Serial No. 09/297,486

Marked-Up Version of Amended Claims

Claim 1 (twice amended):

1. A method for the treatment or prevention of intimal hyperplasia of a blood vessel of a person or animal, where the endothelium of said blood vessel is [wholly or largely] intact, wherein said method comprises periadventitial administration to said blood vessel of said [a] person or animal of an [effective] amount of an agent that is effective to treat or prevent intimal hyperplasia of said blood vessel, wherein said agent comprises a nucleic acid that encodes an agonist of a receptor to which VEGF binds[, or a nucleic acid encoding said agonist] and expressing said agonist encoded by said nucleic acid in the cells of said blood vessel.

Claim 7 (twice amended):

7. The method according to claim 1, wherein said [agent is a protein having the function of human VEGF, or a] nucleic acid encodes a human VEGF [encoding said] protein.

Claim 8 (twice amended):

8. The method according to claim 7, wherein said protein has the sequence of SEQ. ID No. 2, SEQ. ID No. 4, SEQ. ID No. 6 or SEQ. ID No. 8, or [an active] a biologically-active fragment thereof.

Claim 9 (twice amended):

9. The method according to claim 1, wherein said [agent is a] nucleic acid is in association with a viral or non-viral vector.

Claim 14 (amended):

14. A method of therapy for a condition that can be treated or prevented by stimulation of one or both of nitric oxide (NO) [and/or] and prostacyclin production *in vivo*, wherein said method comprises administration to a person or animal of an [effective] amount of an agent that is effective for therapeutic treatment of said condition, wherein said agent comprises [is a nitric oxide synthase,

an agonist of a receptor to which VEGF binds, or] a nucleic acid [encoding said synthase or said] that encodes an agonist of a receptor to which VEGF binds and expressing said agonist encoded by said nucleic acid.